We claim:

1. A cell comprising a disruption in a target DNA sequence encoding a TRP.
2. The cell of claim 1, wherein the disruption is produced by the method comprising:
   (a) obtaining a first sequence homologous to a first region of the target DNA sequence;
   (b) obtaining a second sequence homologous to a second region of the target DNA sequence;
   (c) inserting the first and second sequences into a targeting construct; and
   (d) introducing the targeting construct into the cell to produce a homologous recombinant resulting in a disruption in the target DNA sequence.
3. The cell of claim 2, wherein the method further comprises:
   subsequent to step (b);
   (i) providing a vector having a gene encoding a positive selection marker; and
   (ii) using ligation-independent cloning to insert the first and second sequences into the vector to form the construct;
   wherein the positive selection marker is located between the first and second sequences in the construct.
4. The cell of claim 3, wherein the vector further comprises a gene coding for a screening marker.
5. The cell of claim 1, wherein said target DNA sequence comprises CTG trinucleotide repeats.
6. The cell of claim 5, wherein said CTG trinucleotide repeats encode leucine residues.
7. The cell of claim 1, wherein the target gene sequence is T243 or a naturally occurring allelic variation thereof.
8. The cell of claim 1, wherein the target DNA sequence comprises SEQ ID NO:47.
9. The cell of claim 1, wherein the target DNA sequence comprises SEQ ID NO:45 and SEQ ID NO:46.
10. The cell of claim 3, wherein the vector further comprises one or more recombinase target sites flanking the positive selection marker.
11. The cell of claim 2, wherein the first sequence is SEQ ID NO:50 and the second sequence is SEQ ID NO:51.

12. The cell of claim 2, wherein the first and second sequences are obtained by the method comprising:

(a) obtaining two primers capable of hybridizing with said target, wherein the primers form the endpoints of amplification products;

(b) providing a mouse genomic DNA library containing the target sequence;

(c) annealing said primers to complementary sequences in said library;

(d) amplifying said first and second sequences; and

(e) isolating the products of the amplification reaction.

13. The cell of claim 12, wherein the first primer is SEQ ID NO:45.

14. The cell of claim 12, wherein the second primer is SEQ ID NO:46.

15. The cell of claim 12, wherein said amplification comprises PCR.

16. The cell of claim 15, wherein said amplification further comprises long-range PCR.

17. The cell of claim 12, wherein said mouse genomic library is a plasmid library.

18. The cell of claim 12, wherein said mouse genomic library is a bacteriophage library, said method further comprising obtaining two primers which are capable of hybridizing to bacteriophage vector sequences such that the amplification product terminates at one end with a target sequence primer and at the other end terminates with a vector primer.

19. The cell of claim 1, wherein said cell comprises a homozygous disruption in the target DNA sequence.

20. The cell of claim 1, wherein said cell is murine.

21. The cell of claim 1, wherein said cell is human.

22. The cell of claim 1, wherein said cell is a stem cell.

23. The stem cell of claim 22, wherein said stem cell is an embryonic stem cell.

24. A blastocyst containing the embryonic stem cell of claim 23.

25. The targeting construct used in the method of claim 2.

26. A non-human vertebrate comprising a heterozygous disruption in a gene encoding a TRP.

27. The vertebrate of claim 26, wherein said vertebrate is a mammal.

28. The vertebrate of claim 26, wherein said mammal is a mouse.

29. The mouse of claim 28, wherein said mouse is produced by the method comprising:

(a) incorporating a stem cell of claim 1 or 2 into a blastocyst;

(b) implanting the resulting blastocyst into a pseudopregnant mouse wherein said pseudopregnant mouse gives birth to a chimeric mouse containing the disrupted gene encoding the TRP in its germ line; and

(c) breeding said chimeric mouse to generate a mouse comprising a heterozygous disruption in the gene encoding the TRP.

30. The mouse of claim 28, said mouse produced by the method comprising:

(a) incorporating a stem cell of claim 3 into a blastocyst;

(b) implanting the resulting blastocyst into a pseudopregnant mouse wherein said pseudopregnant mouse gives birth to a chimeric mouse containing the disrupted gene encoding the TRP in its germ line; and

(c) breeding said chimeric mouse to generate a mouse comprising a heterozygous disruption in the gene encoding the TRP.

31. The mouse of claim 28, wherein said TRP is encoded by T243 or a naturally occurring allelic variation thereof.

32. A knockout mouse comprising a homozygous disruption in a gene encoding a TRP, wherein said disruption inhibits the production of the wild type TRP, said mouse produced by mating together two mice according to claim 28.

33. The knockout mouse of claim 32, wherein the disruption alters a TRP gene promoter, enhancer, or splice site such that the mouse does not express a functional TRP.

34. The knockout mouse of claim 32, wherein the disruption is an insertion, missense, frameshift or deletion mutation.

35. The knockout mouse of claim 32, wherein the phenotype of the adult mouse comprises reduced weight relative to a wild type adult mouse.

36. The knockout mouse of claim 35, wherein said phenotype further comprises weight reduced by at least about 15% relative to a wild type adult mouse.

37. The knockout mouse of claim 32, wherein the adult phenotype of the mouse decreased length relative to a wild type adult mouse.

38. The knockout mouse of claim 37, wherein said phenotype further comprises length decreased at least about 10% relative to a wild type adult mouse.

39. The knockout mouse of claim 32, wherein the adult phenotype of the mouse comprises a decreased ratio of weight to length relative to a wild type adult mouse.

40. The knockout mouse of claim 39, wherein said phenotype further comprises a ratio of weight to length decreased at least about 20% relative to a normal, wild type adult mouse.

41. The knockout mouse of claim 32, wherein the phenotype of the adult mouse relative to a wild type mouse adult comprises:

(a) reduced weight;

(b) decreased length; and

(c) decreased ratio of weight to length.

42. The knockout mouse of claim 32, wherein the phenotype of the adult mouse comprises symptoms associated with cartilage disease.

43. The knockout mouse of claim 32, wherein the phenotype of the adult mouse comprises symptoms associated with bone disease.

44. The knockout mouse of claim 32, wherein the phenotype of the adult mouse comprises symptoms associated with kidney disease.

45. The knockout mouse according to claim 41, wherein the phenotype is not apparent at birth.

46. A cell or cell line derived from the mouse of claim 28 or 32 containing said disruption.

47. A method of identifying agents capable of affecting a phenotype of a knockout mouse comprising:

(a) administering a putative agent to the knockout mouse of claim 32;

(b) measuring the response of the knockout mouse to the putative agent; and

(c) comparing the response with that of a wild type mouse;

(d) thereby identifying the agent capable of affecting a phenotype of a knockout mouse.

48. An agent identified according to the method of claim 47.

49. A method of determining whether expansion of the trinucleotide repeat in a gene encoding a TRP produces a phenotypic change comprising:

(a) providing the knockout cell of claim 10 and a synthetic nucleic acid comprising trinucleotide repeats flanked by recombinase target sites;

(b) contacting said knockout stem cell with said synthetic nucleic acid in the presence of a recombinase which recognizes said recombinase target sites, such that recombination occurs between the synthetic nucleic acid, thereby producing a transgenic cell; and

(c) comparing the phenotype of said transgenic cell with a wild type cell;

thereby determining whether trinucleotide expansion produces a phenotypic change.

50. The method of claim 49, wherein said trinucleotide repeats comprise CTG.

51. The method of claim 49, wherein said method comprises the use of a Cre recombinase-lox target system.

52. The method of claim 49, wherein said method comprises the use of a FLP recombinase-FRT target system.

53. A knockout cell or cell line comprising a disruption in a target DNA sequence encoding a TRP.

54. The knockout cell or cell line of claim 53, wherein said cell is derived from the mouse of claim 32.

55. Tissue derived from the mouse of claim 28 or 32.

56. The knockout cell of claim 53 wherein the TRP is encoded by T243 or a naturally occurring allelic variation thereof.

57. A method of identifying agents capable of affecting a phenotype of a knockout cell line comprising:

(a) contacting the knockout cell of claim 53 with a putative agent;

(b) measuring the response of the cell to the putative agent; and

(c) comparing the response with that of a wild type cell;

(d) thereby identifying the agent capable of affecting a phenotype of a knockout cell.

58. A cell line comprising a nucleic acid sequence encoding a TRP operably linked to a promoter functional in said cell line.

59. The cell line of claim 58, wherein the TRP is encoded by T243 or a naturally occurring allelic variation thereof

60. The cell line according to claim 59, wherein the TRP consists essentially of the amino acid sequence **SEQ ID NO:52** or a naturally occurring allelic variation thereof.

61. The Trinucleotide Repeat Protein encoded by T243 or a naturally occurring allelic variation thereof.

62. A murine TRP consisting essentially of the sequence of SEQ ID NO:52 or a naturally occurring allelic variation thereof.

63. A human TRP consisting essentially of the sequence of SEQ ID NO:58 or a naturally occurring allelic variation thereof.

64. A nucleic acid sequence encoding the murine TRP of claim 62, of the sequence SEQ ID NO:47 or a naturally occurring allelic variation thereof.

65. A nucleic acid sequence encoding the human TRP of claim 63, of the sequence SEQ ID NO:47 or a naturally occurring allelic variation thereof.

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